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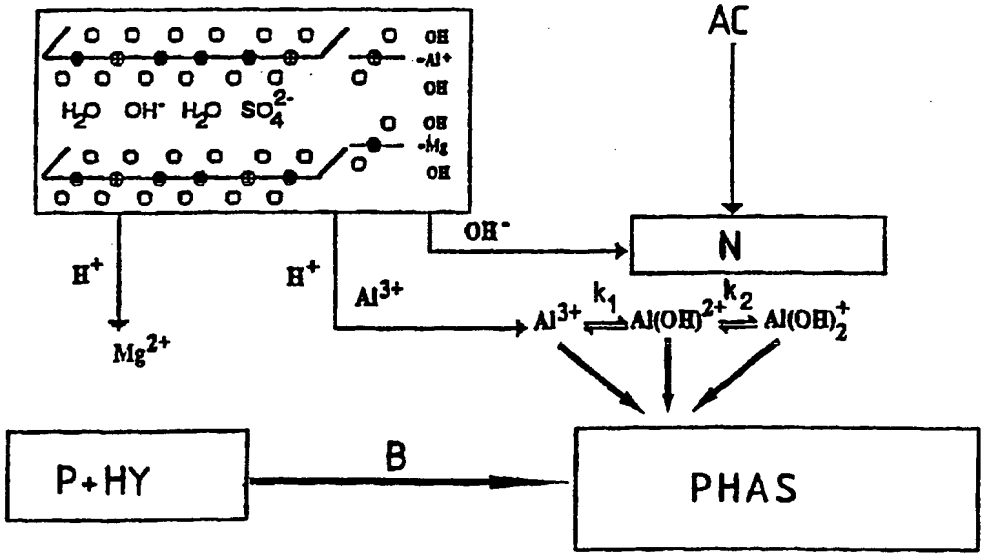

(57) Abstract

A pharmaceutical preparation containing at least one aluminium compound for antacid and/or abstringent and adsorbent actions is manufactured by treating 2-300 parts by weight of a water-swellable compound of limited swelling ability with 2-50 parts by weight of water and thereafter admixing it with a powder comprising at least one of the group consisting of 100 parts by weight of said at least one aluminium compound, 2-150 parts by weight of at least one phosphate compound and at least one auxiliary material. The mixture may be granulated and dried, and thereafter either pressed to tablets or filled into capsules; it may also be transformed into a suspension.

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Aluminium containing pharmaceutical preparation with controlled release

FIELD OF THE INVENTION

The invention relates to an antacid and/or adstringent and absorbent pharmaceutical preparation containing at least one aluminium compound, as well as a process for the production of such preparations.

BACKGROUND OF THE INVENTION

The disequilibirum between protective and aggressive factors, such as hydrochloric acid, pepsin, bile acid, lysolecithin, nicotine, alcohol, stress, Helicobacter pylori etc. leads to different pathogenic events, such as ulcer, in the gastroduodenal area. Most antacid preparations used for the treatment of ulcer and pre-ulcer hyperacidity contain aluminium compounds. However, when aluminium is taken into the organism and absorbed, this may cause osteomalacia, osteodystrophia, neuropathy, Alzheimer disease etc. These disadvantages are described by C.Gitzinger, Fortschritte der Medizin, 105, 3/Suppl.19/,1987; and by W.Kurtz, ibid. 105, 5/Suppl.19/,1987.

According to EP-A1-220,849, the probability of aluminium absorption and hence of unwanted side effects is increased with decreasing the final pH in the aluminium-based (e.g. aluminium hydroxide, magnesium-aluminium-hydrate, magaldrate etc.) liquid preparation (oral suspension) to pH=2.20-3.25 assuming cytoprotective effects.

According to US-A-4,704,278, the same consequence occurs when the system contains a significant amount of citrate, which is added partly from a colloidal point of view, partly to ensure a quick start of the action. All factors increas-

ing the solubility of aluminium compounds, such as the citrate ion, increase the risk of aluminium absorption.

The process according to US-A-4,639,362 proposes combined molecules of magnesium and aluminium components such as magaldrate), in which the aluminium content is lower than in the usual antacid formulae. On the other hand, the higher magnesium content may result in an undesired laxative effect.

It has therefore been one object of the invention to provide an antacid and/or adstringent and absorbent pharmaceutical preparation which avoids the drawbacks related to the absorption of aluminium in the body of a patient. Another object of the invention relates to the provision of a pharmaceutical preparation with sustained release of the antacid and/or adstringent and absorbent compounds.

SUMMARY OF THE INVENTION

These objects are achieved by the inventive measures based on the surprising novel recognition that the dissolution of absorbable aluminium in aqueous media can significantly be decreased or completely inhibited by applying certain types of macromolecular hydrocolloids and water-soluble and/or water-insoluble phosphate compounds in the presence of each other.

This phenomenon was observed in every case, i.e. in a tablet as well as in a suspension preparation, when the aluminium compound was applied and treated in mixture with at least one hydrocolloid of limited swelling ability and at least one water-soluble and/or water-insoluble phosphate compound, resulting in a limited or inhibited aluminium release due to the contact with gastric fluids by swelling of the hydrocolloid. The limited swelling ability is influenced by the pH and the presence of Al^{3+} and can be characterized for the

various hydrocolloids by viscosimetry. Usually, about 10% of the hydrocolloids - given as examples hereinafter - are indeed swelled.

The principle of the invention is a phosphate delivery system controlled by the swelling mechanism of the hydrocolloid.

BRIEF DESCRIPTION OF THE DRAWINGS

In Fig.1, the top left rectangle symbolizes the magaldrate example. Excess acid (AC) in the gastric fluid is neutralized (N) by the OH^--flux. The resulting Al^{3+}-flux is bound by the phosphate P and the swelled (arrow B) hydrocolloid HY to the phosphate/hydrocolloid/aluminium system (PHAS). The phosphate/hydrocolloid system (P+HY) controls the dissolution and binding of the aluminium as shown in

Fig.2 (left of the dotted line: stomach ST; right of the dotted line: intestines IN) partly through an oscillating reaction mechanism influenced by the change of the intragastric pH-value, partly by binding the aluminium to the hydrocolloid, advantageously to a crosslinked polymer.

Fig.3 shows the principle of the aluminium capture based partly on the significant difference in the solubility of aluminium hydroxide and aluminium phosphate; partly, it is also based on the function of the hydrocolloid-phosphate system, which binds the aluminium and is activated by the swelling of the hydrocolloid. The described aluminium capturing system does not decrease the acid neutralization capacity of the aluminium compound at the acidic pH of the stomach (ST) but inhibits the absorption of aluminium from the stomach (ST) and the duodenum (intestines (IN), see Fig.2) of higher pH.

Fig.4 demonstrates the function of the control mechanism by experimental observations obtained from the pH-potentiometric titration. When titrating 500 ml of a 0.01 M HCl solution (pH=2) with 1.0 M NaOH in the presence of several components ($AlCl_3$, Nymcel ZSB10(R) as hydrocolloid of limited swelling ability, NaH_2PO_4.2aq), the potentiometric curves differ. Curve 1 designates 500 ml 0.01 N HCl solution containing 0.01 mol $AlCl_3$; Curve 2 designates 500 ml 0.01 N HCl solution containing 0.01 mol $AlCl_3$ and 0.001 mol NaH_2PO_4; Curve 3 designates 500 ml 0.01 N HCl solution containing 0.01 mol $AlCl_3$ and 1 g Nymcel ZSB-10(R); Curve 4 designates 500 ml 0.01 N HCl solution containing 0.01 mol $AlCl_3$, 1 g Nymcel ZSB-10(R) and 0.001 mol NaH_2PO_4.The inflexion point of the potentiometric curve is at much lower alkali consumption in the case of the $AlCl_3$-hydrocolloid-phosphate components.

In vivo experimental data of human male volunteers demonstrate the decrease in the aluminium absorption (Table 1): The mixture according to the invention may be prepared by first swelling the water-swellable compound of limited swelling ability in water and thereafter admixing thereto or embedding in it a powder comprising at least one of the group consisting of 100 parts by weight of aluminium compound, 2-150 parts by weight of at least one phosphate compound, and at least one auxiliary material. The proper combination of the hydrocolloid with the phosphate compound results in the desired sustained release effect.

On the other hand, a tablet preparation may also be produced wherein the components are mixed under dry conditions whereby the swelling and sustained release occurs in the digestive system. On the other hand, the final mixture may be transformed into a suspension or filled into capsules.

Table I. - Change of the aluminium amount excreted by the urine of 5 patients over 24 hours after administration of 750 mg magaldrate compared to the control value of the previous day:

Subject	µg Al/24 h eliminated by urine	
	magaldrate	magaldrate with the phosphate-hydrocolloid system acc. example 3
#1	+ 13.8	+ 8.6
#2	+ 19.2	+ 9.0
#3	+ 4.0	- 7.1
#4	+ 13.0	- 22.2
#5	+ 18.0	+ 14.0
Average:	+ 13.6	+ 0.46
s_x (S.E.M)	2.677 µg	6.683 µg
t-value experimental	5.081	0.0688
Probability	<0.05	>0.05
Difference	significant	not significant

s_x (S.E.M.) is the standard deviation of the mean value; the t-value is the Student-t at 5% significance level.

The aluminium compound may be selected from a wide range of inorganic and organic salts or complex compounds, such as aluminium hydroxide, aluminium glycinate (dihydroxyaluminium aminoacetate hydrate, USP XXII p. 445), aluminiumsodium trisilicate, aluminium hydroxycarbonate (dihydroxyaluminium sodium carbonate, USP XXII p.447), basic aluminium carbonate gel (USP XXII p.50), aluminium phosphate (USP XXII p.53), aluminium magnesium silicate (B.P.), natural or synthetic aluminium- and magnesium-containing compounds, preferably aluminiummagnesium hydroxycarbonate (hydrotalcite) and aluminiummagnesium hydroxysulphate (magaldrate).

The water-swellable compounds may be selected from the group comprising cellulose glycolic acid, starch glycolic acid, polyacrylic acid, copolymers of acrylic acid-methacrylic acid, alginic acid (polymannuronic acid, USNF XVII), poly-

vinylpyrrolidone, calcium alginate (BPC), sodium alginate (USNF XVII), Carbopol(R) 934P (carbomer, USNF XVII), carboxymethylcellulose calcium (USNF XVII), carboxymethylcellulose sodium (carmellose, USP XXII), carrageenan (USNF XVII), croscarmellose sodium (USNF XVII,Ac-Di-Sol(R)), cross-linked polyvinylpyrrolidone (USNF XVII, Polyplasdone XL(R)), hydroxypropylmethylcellulose (USP XXII), carboxymethylcellulose sodium of low substitution grade (Nymcel ZSB-10(R)), sodium starch glycolate (USNF XVII, Primojel(R)), tragacanth (USNF XVII), xanthan gum (USNF XVII).

The phosphate compound may be selected from the group comprising mono-, di- and tribasic calcium phosphate; mono-, di- and tribasic magnesium phosphate; mono- and dibasic sodium phosphate; mono- and dibasic potassium phosphate; mono- and dicalcium glycerophosphate.

Auxiliary materials may be disintegrants such as starch, microcellulose, cross-linked polyvinylpyrrolidone etc.; tableting aids, such as lubricants, e.g. talc, magnesium stearate etc.; sweeteners such as saccharose, glucose, saccharin-sodium, sodium cyclamate, aspartame etc.; flavouring agents such as lemon, orange and cassis aroma; fillers such as lactose.

DETAILED DESCRIPTION OF THE INVENTION

The invention is further explained by way of the following examples.

Example 1

500g hydrotalcite and 70g tribasic calcium phosphate powder (components of the inner phase) are homogenized. 90g of cross-linked polyvinylpyrrolidone are swelled with 60-75 ml water (required for wet granulation) during 2 hours and then mixed with the powder mixture and kneaded. The wet mass is granulated by passing it through a sieve with openings of

1.4 mm. The granules are dried to a moisture content of 2.5% and then regranulated through a sieve with openings of 0.8 mm. 10g of cross-linked polyvinylpyrrolidone, 20g talc and 10g magnesium stearate (powder components of the outer phase) are passed through a sieve with openings of 0.32 mm and mixed with the dry granules. The mixture is compressed to give 1000 tablets each of 0.7 g average weight.

Example 2

The same procedure is followed as in Example 1 with the following compounds (for 1000 tablets of 0.75 g average weight each):

Inner phase:	aluminium hydroxycarbonate	600 g
	tribasic magnesium phosphate	34 g
	carboxymethylcellulose sodium of low substitution grade	10 g
	cross-linked carboxymethyl-cellulose sodium (Ac-Di-Sol(R))	10 g
	water	80-100 ml
outer phase:	potato starch (disintegrant)	50 g
	talc	24 g
	magnesium stearate	12 g
	Nymcel ZSB 10(R)	10 g

Example 3

The same procedure is followed as in Example 1 with the following compounds (for 1000 tablets of 1.3 g average weight each):

Inner phase:	magaldrate	750 g
	dibasic calcium phosphate	450 g
	Nymcel ZSB 10(R)	273 g
	water	80-100 ml
outer phase:	magnesium stearate	25 g
	Nymcel ZSB 10(R)	200 g
	water	80-100 ml

Example 4:

The same procedure is followed as in Example 1 with the following compounds (for 1000 tablets for 1.5 g average weight each):

Inner phase:	aluminium hydroxide	375 g
	tribasic calcium phosphate	100 g
	Nymcel ZSB 10(R)	200 g
	water	80-100 ml
outer phase:	microcrystalline cellulose Avicel PH 102(R)	825 g

Example 5

The same procedure is followed as in Example 4 with the following compounds (for 1000 tablets of 1.5 g average weight each), with the exception that double-layered tablets are formed. The antacid active ingredient is pressed as the first layer, onto which the second layer containing the other components and the microcrystalline cellulose is pressed:

First layer:	aluminium hydroxide	375 g
	microcrystalline cellulose (Avicel PH 102(R))	400 g
second layer:	Nymcel ZSB 10(R)	200 g
	tribasic calcium phosphate	100 g
	water	80-100 ml
	microcrystalline cellulose (Avicel PH 102(R))	425 g

Example 6

The same procedure is followed as in Example 4 - with the exception that three-layered tablets are formed - with the following compounds (for 1000 tablets of 1.5 g average weight each):

First layer:	Aluminium hydroxide	375 g
	microcrystalline cellulose (Avicel PH 102(R))	400 g
second layer:	Nymcel ZSB 10(R)	200 g
	microcrystalline cellulose (Avicel PH 102(R))	250 g
	water	80-100 ml
third layer:	tribasic calcium phosphate	100 g
	microcrystalline cellulose (Avicel PH 102(R))	175 g

Example 7

The same procedure is followed as in Example 4 - with the exception that the particles of the phosphate compound are coated by spraying on them (and afterwards drying) an isopropanolic solution of Eudragit L100-55 - with the following compounds (for 1000 tablets of 1.5 g average weight each):

Inner phase (aluminium):		
	aluminium hydroxide	375 g
inner phase (phosphate):		
	tribasic calcium phosphate	100 g
coating:		
	Eudragit L 100-55[6]	7.5 g
	isopropanol	60 g
	Nymcel ZSB 10(R)	200 g
	water	80-100 ml
outer phase:	microcrystalline cellulose (Avicel PH 102(R))	825 g

Example 8

The same procedure is followed and composition used as in Example 7 with the exception that the tribasic calcium phosphate is coated with a solution of 4.5 g celluloseacetatephtalate in 30 ml of acetone.

Example 9

1000 ml of an antacid suspension are prepared, having the following composition:

magaldrate	200 g
cross-linked carboxymethylcellulose sodium (Ac-Di-Sol(R))	50 g
tribasic calcium phosphate	75 g
tribasic magnesium phosphate	75 g
hydroxy-propylmethylcellulose 4000	12 g
methylparaben	10 g
alcohol	10 g
water, deionized	to 1000 ml

Ac-Di-Sol(R) is swelled in a 2% solution of the viscosity increasing agent HPMC 4000 (viscosity 4000 cP); then, the homogenous mixture of the various powder components is suspended in it. Finally, the alcoholic solution of the microbiological preservative (methylparaben) is added.

Example 10

Example 9 is repeated except that the composition differs as follows:

aluminium hydroxide	100 g
alginic acid	140 g
monobasic sodium phosphate	140 g
hydroxy-propylmethylcellulose 4000	12 g
propylparaben	2.5 g
methylparaben	2.5 g
alcohol	10 g
water, deionized	to 1000 ml

The alginic acid is first swelled in the acidic hydroxy-propylmethylcellulose solution containing monobasic sodium phosphate to produce the limited swelling form of the hydrocolloid.

Example 11

The following powder components for 1000 capsules:

aluminium hydroxide	250 g
monobasic sodium phosphate	100 g
alginic acid	100 g

are mixed and granulated in the dry state or by adding water and drying; then, 0.5 g Aerosil R972(R) lubricant is mixed with the dry granules. A 0.40-0.45 g portion of the mixture is filled into a hard gelatine capsule.

Example 12

A tablet preparation with antacid and adstringent effect is formulated with the following composition for 1000 tablets:

aluminium hydroxide	500 g
aluminium glycinate	500 g
cellulose glycolic acid	250 g
Carbopol 934P(R)	25 g
tribasic magnesium phosphate	100 g
magnesium stearate	23 g
Aerosil R972(R)	2 g

The process is completed in the usual way: the cellulose glycolic acid is swelled in the Carbopol 934P(R) solution. This liquid is used for the wet granulation of the powder mixture. The tablet preparation is formed as described in Example 1.

C L A I M S

1. Process for the manufacture of a pharmaceutical preparation containing at least one aluminium compound for antacid and/or adstringent and absorbent action, wherein 2-300 parts by weight of a water-swellable compound of limited swelling ability selected from the group consisting of the dry compound and the compound after treatment with 2-50 parts by weight of water is admixed with 100 parts by weight of said at least one aluminium compound and 2-150 parts by weight of at least one phosphate compound.

2. Process according to claim 1, wherein at least one auxiliary material selected from the group consisting of tableting vehicles, diluents, sweeteners and flavouring agents is further added to the mixture.

3. Process according to claim 1 or 2 wherein the mass is granulated and dried.

4. Process according to claim 1, wherein said aluminium compound is selected from the group consisting of aluminium hydroxide, aluminium glycinate (dihydroxyaluminium aminoacetate hydrate), aluminiumsodium trisilicate, aluminium hydroxycarbonate (dihydroxyaluminium sodium carbonate), basic aluminium carbonate gel, aluminium phosphate, aluminium magnesium silicate, natural or synthetic aluminium- and magnesium-containing compounds, such as aluminiummagnesium hydroxycarbonate (hydrotalcite) and aluminiummagnesium hydroxysulphate (magaldrate).

5. Process according to claim 1, wherein said water-swellable compound is selected from the group consisting of cellulose glycolic acid, starch glycolic acid, polyacrylic acid, copolymers of acrylic acid-methacrylic acid, alginic acid, polyvinylpyrrolidone, calcium alginate,

sodium alginate, carbomer, carboxymethylcellulose calcium, carboxymethylcellulose sodium (carmellose), carrageenan, croscarmellose sodium, hydroxypropylmethylcellulose, carboxymethylcellulose sodium of low substitution grade, sodium starch glycolate, tragacanth and xanthan gum.

6. Process according to claim 1, wherein said phosphate is selected from the group consisting of mono-, di- and tribasic calcium phosphate; mono-, di- and tribasic magnesium phosphate; mono- and dibasic sodium phosphate; mono- and dibasic potassium phosphate; mono- and dicalcium glycerophosphate.

7. Process according to claim 6, wherein the particles of said phosphate are coated - per 100 parts by weight of said phosphate compound(s) - with 2.5 to 15 parts by weight of a sustained release coating material.

8. Process according to claim 1, wherein the mixture is further granulated and dried.

9. Process according to claim 8, wherein the dried mixture is pressed to tablets.

10. Process according to claim 8, wherein the dried mixture is filled into capsules.

11. Process according to claim 1, wherein the mixture is further transformed into an aqueous suspension.

12. Pharmaceutical preparation containing at least one aluminium compound for antacid and/or adstringent and absorbent action, wherein said aluminium compound is present in admixture with at least one water-swellable compound selected from the group consisting of hydrocolloids, synthetic polymers and natural polymers, and with at least one pharmaceutically acceptable phosphate compound.

13. Pharmaceutical preparation according to claim 12, wherein said aluminium salt is selected from the group consisting of aluminium hydroxide, aluminium glycinate (dihydroxyaluminium aminoacetate hydrate), aluminiumsodium trisilicate, aluminium hydroxycarbonate (dihydroxyaluminium sodium carbonate), basic aluminium carbonate gel, aluminium phosphate, aluminium magnesium silicate, natural or synthetic aluminium- and magnesium-containing compounds, such as aluminiummagnesium hydroxycarbonate (hydrotalcite) and aluminiummagnesium hydroxysulphate (magaldrate).

14. Pharmaceutical preparation according to claim 12, wherein said water-swellable compound is selected from the group consisting of cellulose glycolic acid, starch glycolic acid, polyacrylic acid, copolymers of acrylic acid-methacrylic acid, alginic acid, polyvinylpyrrolidone, calcium alginate, sodium alginate, carbomer, carboxymethylcellulose calcium, carboxymethylcellulose sodium (carmellose), carrageenan, croscarmellose sodium, hydroxypropylmethylcellulose, carboxymethylcellulose sodium of low substitution grade, sodium starch glycolate, tragacanth and xanthan gum.

15. Pharmaceutical preparation according to claim 12 wherein said phosphate compound is selected from the group consisting of mono-, di- and tribasic calcium phosphate; mono-, di- and tribasic magnesium phosphate; mono- and dibasic sodium phosphate; mono- and dibasic potassium phosphate; mono- and dicalcium glycerophosphate.

16. Pharmaceutical preparation according to claim 12 or 15, wherein the particles of said phosphate compound(s) are coated - per 100 parts by weight of said phosphate compound(s) - with 2.5 to 15 parts by weight of a sustained release coating material.

17. Pharmaceutical preparation according to claim 12, further comprising at least one auxiliary compound selected from the group consisting of tableting vehicles, diluents, sweeteners and flavouring agents.

18. Pharmaceutical preparation according to claim 12, wherein any one compound of the group consisting of the aluminium compound, the phosphate compound and the auxiliary material is embedded in said swellable compound.

19. Pharmaceutical preparation according to claim 12, characterized in that it is in the form of a tablet.

20. Pharmaceutical preparation according to claim 12, characterized in that it is in the form of a suspension.

21. Pharmaceutical preparation according to claim 12, characterized in that it is contained in a capsule.

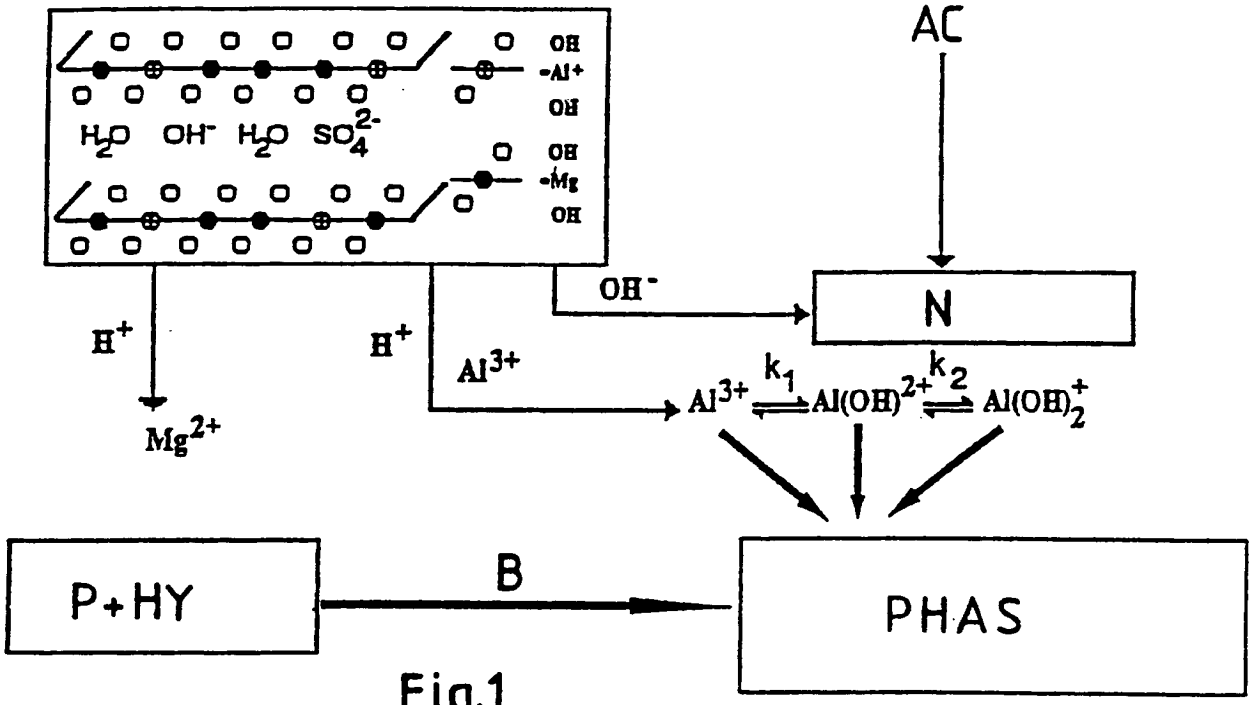

Fig.1

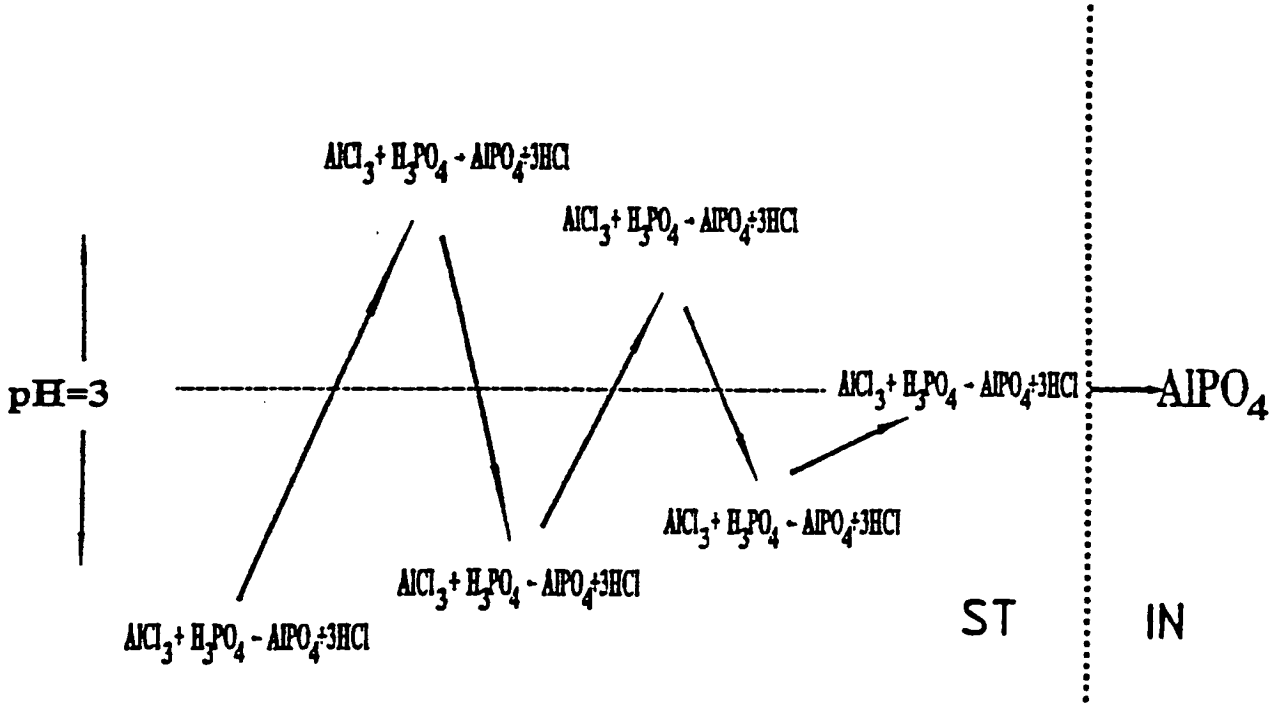

Fig.2

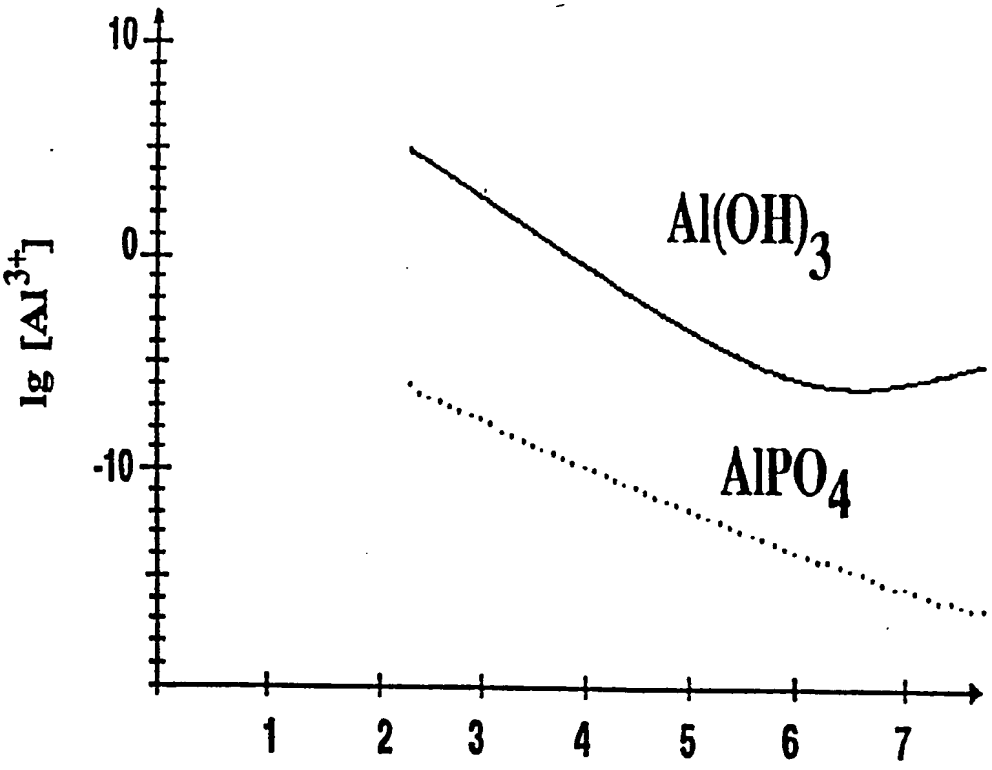

Fig.3

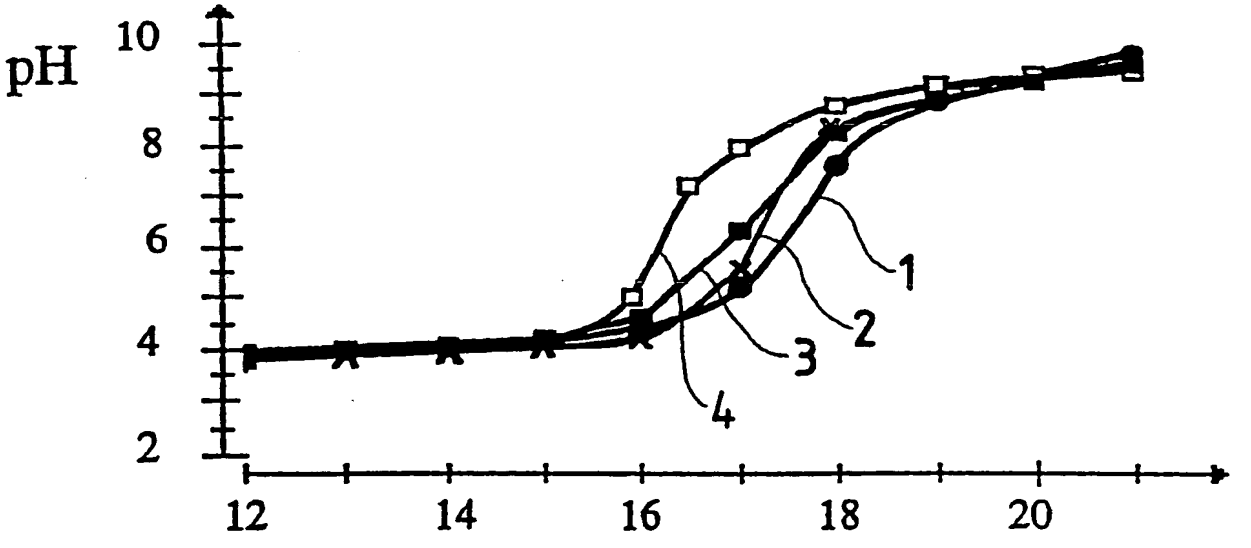

Fig.4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 94/00829

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K33/08 A61K33/10 A61K9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP,A,0 003 589 (THE WELLCOME FOUNDATION LIMITED) 22 August 1979 see the whole document see page 16 - page 17; example 4 ---	12-21 1-11
X	FR,A,2 512 344 (LABORATORIOS A.F. APLICACIONES FARMACEUTICAS SA.) 11 March 1983 see page 6 - page 7; example 1 ---	12-15, 17,20
X	US,A,3 591 680 (GREENE ET AL.) 6 July 1971 see column 5; example 2 ---	12-15, 17,20
Y	WO,A,88 00051 (RACZ ET AL.) 14 January 1988 see the whole document ---	1-21
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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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